Genetic testing for melanoma

Inherited mutations in either the *CDKN2A* or *CDK4* gene contribute to melanoma susceptibility in carriers. The *CDKN2A* gene encodes two important cell-cycle regulatory proteins, p16 and p14ARF. The Melanoma Genetics Consortium (which consists of most of the research groups worldwide that have published research on germline mutations in melanoma families) has previously published a consensus statement on genetic testing for melanoma. This statement recommended that such testing should only be carried out in the context of clinical research.[1] Recently, however, because of the vigorous promotion of a commercially available DNA test for *CDKN2A* mutations, and the availability of new data on the incidence of melanoma in mutation carriers ("penetrance"),[2] the Consortium has reviewed its original recommendations. In light of these new developments, the Consortium still recommends that it is premature to offer *CDKN2A* testing.

CDKN2A germline mutations are rare and many only underlie melanoma susceptibility in a very small proportion of the general population. The majority of the genetically predisposed people within the population are at a high risk for other reasons such as: a family history of melanoma (ie, the presence of two or more melanoma-affected relatives on the same side of the family); the presence of large numbers of common or atypical naevi; a history of primary melanoma or non-melanoma skin cancers; immunosuppression; skin that burns readily in response to sunlight and fails to tan; freckling; blue eyes; red hair; or a history of blistering sunburn. Such individuals should be counselled about sun avoidance and self examination, and a judgement made as to the necessity of enrollment in to a programme of prevention and surveillance.[1]

Some of these individuals will be at particularly high risk and may carry inherited mutations in highly penetrant melanoma susceptibility genes such as *CDKN2A* and *CDK4*; however, the actual likelihood of mutations being found is very low. Mutation markers generally have poor predictive power but examples include: family history of melanoma in four or more individuals (and, in certain kindreds, pancreatic cancer or, rarely, neural tumours); occurrence of cutaneous melanoma at an early age; and presence of multiple primary melanomas. The presence of multiple naevi, whether atypical or not, is also a risk factor for melanoma, but it is not predictive of mutations in the *CDKN2A* or *CDK4* gene.[3,4]

We suggest that genetic testing for melanoma is of limited clinical utility because of the following reasons:

- Even in large multicase families, over 60% of high-risk melanoma kindreds have, as yet, no identifiable genetic basis, and research screening suggests that the prevalence of *CDKN2A* mutation carriers is less than 1% in high-incidence populations.[5] As a result, no mutations will be identifiable in the majority of families presenting to clinical geneticists.
- The confidence limits on current estimates of lifetime penetrance of *CDKN2A* mutations are very broad and penetrance varies widely with locality, which could reflect the influence of ambient ultraviolet radiation on phenotypic expression of the mutation, or the influence of other gene–gene or gene–environment factors. Thus, our current estimate of the risk of acquiring melanoma before the age of 80 years in carriers of *CDKN2A* mutations is 53% in Europe and 91% in Australia. In contrast, the comparable risk before 50 years is 13% and 32%, respectively.[2]
- Even within large melanoma families carrying *CDKN2A* mutations, a negative genetic test may give false security because there is evidence to suggest that non-carriers of mutations in these families may have a higher incidence of melanoma than the general population; presumably due to co-inheritance of other less penetrant susceptibility genes and common environmental risks among family members. Consequently, in families with inherited *CDKN2A* mutations, 9% of melanoma cases occur in individuals that do not carry these mutations. Conversely, certain gene carriers, who live a long time, do not develop melanoma,[6] and unaffected individuals, homozygous for a *CDKN2A* mutation, have also been identified.[7] This suggests that there are other genes and environmental factors affecting the penetrance of *CDKN2A* mutations. Mutations in the other known melanoma susceptibility gene, *CDK4*, are even less well studied because of the small number of identified affected families.[8]
- The risk of cancers other than melanoma in *CDKN2A* gene carriers is not yet known.

The Consortium concludes that it is premature to offer genetic testing for mutations in *CDKN2A* in families, or in individuals with multiple primary melanomas, outside of defined research protocols. Only in exceptional rare circumstances should tests be offered, and only then, after careful genetic counselling to adequately address the low likelihood of finding mutations, the current uncertainties about the risk and expression of specific mutations, the potential benefits and risks of positive and negative results, and the absence of evidence-based melanoma prevention and screening strategies. These conclusions are based on data that are derived largely from families in fair-skinned populations in which the incidence of melanoma is high (for example, Australia, USA, and Scandinavia).

Many different healthcare systems exist among the members of the Consortium and therefore different issues and approaches to care-delivery arise. In countries of low melanoma incidence, or where founder mutations are prevalent and contribute to the observed familial clusters (currently defined as two or more affected family members),[9,10] it is possible that DNA testing may improve compliance with sun protection and surveillance in mutation carriers. Until further data become available, however, clinical evaluation of risk remains the gold standard for preventing melanoma. First-degree relatives of individuals at high risk should be engaged in the same programmes of melanoma prevention and surveillance irrespective of the results of any genetic testing.

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Tamoxifen non-compliance: does it matter?

Non-compliance during long-term drug therapy is a recognised health problem. This was the underlying reason for the Direct Observation Treatment, Short-Course (DOTS) scheme introduced by WHO to counter drug resistance and treatment failure during therapy for tuberculosis.[1] However, in the cancer arena, little is known about the prevalence of non-compliance during long-term administration of tamoxifen, the reason behind it, and ultimately, what effect non-compliance has on breast-cancer mortality.[2] Since the survival benefit depends on the duration of tamoxifen use,[3] non-compliance may dilute the efficacy by reducing the total duration of ‘active’ treatment and possibly inducing tamoxifen resistance.[4]

To generate background data for a large prospective study, we have recently done a survey of tamoxifen compliance using a self-report questionnaire in 53 randomly selected women. 62% of the women had missed tamoxifen in the last 6 months, whereas 38% reported that they had not missed a single dose. Of the 33 women who admitted to non-compliance, 37% missed one dose per month, 24% two or three doses per month, 24% one or two a week, and 15% more frequently. Overall, 24% missed tamoxifen once or more per week (major non-compliance). This may be an underestimate, because self-report measures substantially over-estimate the compliance rates compared with more objective methods such as pill-counts and microelectronic monitoring.[5] In our study, age, socioeconomic parameters, and duration of tamoxifen use were not found to be significant determinants of major non-compliance, possibly because of the small sample size. However, the most common reason cited by patients was that they had simply forgotten to take the medicine, although two patients had major non-compliance due to religious fasting.

Since tamoxifen non-compliance may be more frequent than perceived, there is a need to reliably estimate both its incidence and its cause so that criteria defining major and minor violations can be established. This may help unravel the multifactorial problem of non-compliance, the identification of patient groups that are likely to default, and the derivation of strategies to improve compliance. More importantly, it may give us an opportunity to explore alternate approaches of hormonal manipulation in specific patient populations and ensure that efficacy of this widely used drug is maintained in the long term.

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